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Cost saving and predictive factors of response to rituximab in rheumatoid arthritis, including the IL-6 promoter gene polymorphism

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ABSTRACT

BACKGROUND: to evaluate quality of life (QoL) and cost/utility when using predictors of response in a real-life cohort of rheumatoid arthritis (RA) patients treated with rituximab and followed for one year. A recently reported pharmacogenetic predictor of response was included.

METHODS: this was a retrospective study in patients with established RA. The goal of this study was to understand the possible economic usefulness of the predictors of response in RA treated with rituximab. Information on QoL was collected at baseline, at month +6 and +12. Cost/QoL gained were also derived. Rheumatoid factor, number of TNF blockers previously failed (positive predictors) and the -174 CC interleukin-6 (IL-6) promoter genotype (negative predictor) were considered as predictive factors of response to rituximab.

RESULTS: 66 patients (54 females, 12 males) with RA were treated with rituximab at standard regimen. Retreatment with rituximab was given at clinical relapse. Rituximab was generally used after failure of anti-TNFalpha agents (81.8%). 96 courses of rituximab were administered during 12 months. Cost/QoL gained was € 56 589.50 at month +12. Patients carrying predictors (≥2 out of 3) (28/66 patients) showed a cost/QoL gained of € 44 279.10 at month +12. Thirty-four courses of rituximab were administered in this group (1.21±0.42). Patients without predictors (≤1 out of 3) (38/66 patients) showed a cost/QoL gained of € 66 769.23 at month +12. 62 courses of rituximab were administered in this group (1.63±0.59). The number of courses of rituximab during one year significantly differed between the two groups (p=0.003).

CONCLUSIONS: predictors of response to rituximab selected those patients who need a lesser amount of rituximab during the first year after treatment. Cost/utility of rituximab in established RA may be optimized by using predictors of response, possibly including pharmacogenetic markers.

Key words: Rheumatoid arthritis, Rituximab, Pharmacogenetic, Quality of life, Biologics

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INTRODUCTION

Rheumatoid arthritis (RA) is one of the most frequent autoimmune diseases in the world, with prevalence in Italy of about 0.5% (1). The socioeconomic costs of RA are very high, and the indirect costs are prevalent (2). Several biologic therapies with different biologic targets (i.e., tumor necrosis factor (TNF) alpha, interleukin-1, interleukin-6 (IL-6), CD20 positive B cells, activated T lymphocytes), are now available for moderate to severe RA (3), and phase II or III studies are in course for many others (4). However, the cost of these therapies is very high, and, besides the international guidelines for the use of biologic disease-modifying antirheumatic drugs in RA (3), the identification a priori of the best biologic therapy in the single patient is still impossible (5). Research is however ongoing to identify predictive factors of response to the different biologics (6).

Rituximab is a chimeric monoclonal antibody (ch-IgG1k) directed against CD20, an antigen expressed by most B cells (7). It is approved, as a second line after anti-TNF failure, for the treatment of RA (8-10). Clinical, laboratory and possibly genetic factors have been associated with early response (i.e. at month +6 after initial treatment) to rituximab in RA (11), with contributions on this topic also by our Group (12, 13). However, the usefulness of these predictive factors on the costs of RA has not yet been reported. Thus, the aim of this study is to evaluate quality of life (QoL) and cost/utility of rituximab in 66 real-life longstanding difficult-to-treat RA patients in a follow-up of 12 months after treatment, when predictive factors of response are applied. Notably, one recently reported pharmacogenetic predictor was included in the analyses.

METHODS

The study was designed as a retrospective study in an unselected cohort of patients with established RA diagnosed according to the 1987 American College of Rheumatology (ACR) classification criteria (14), and treated with rituximab at standard dose for RA (two 1 000 mg infusions administered two weeks apart: one cycle of treatment) in four Italian Clinics involved in the cure of the rheumatic diseases. Retreatment with rituximab at standard dose (two 1 000 mg infusions administered two weeks apart) was given at the time of clinical relapse, as recommended (15). Patients were followed for at least 12 months after rituximab treatment. All the patients were taking no glucocorticoids, or <10 mg/day of prednisone or equivalent at baseline.

Type of cost considered in our study was rituximab cost acquisition (€ 5 600 for one cycle of treatment) (Table 1). No other costs were considered. Information on Quality of Life (QoL) as utility, derived from the Health Assessment Questionnarie Disability Index (HAQ-DI) (16), was collected at baseline, at month +6 and +12. Then, the QoL gained was calculated by comparison with baseline QoL. The following algorithm was used to

TABLE 1

STUDY DESIGN AND TYPE OF COSTS	
Study design	Retrospective multicenter
Population	Established rheumatoid arthritis (≥2 years of disease duration)
Time horizon	First year after rituximab therapy
Type of costs/category	Direct medical costs/pharmaceutical costs*
Year/currency of costs	2010/EURO
Source of data	National tariffs and subsequent hospital tender price (plus 10% of V.A.T.)

Legend: V.A.T., value added tax

*only costs of rituximab have been considered

derive utility (Health Utility Index-III, HUI-3) from HAQ: HUI-3 utility=0.76-0.286*HAQ-DI + 0.056*FEMALE (16). The HUI-3 has been validated as a good measurement for severe diseases, even this validation has not yet been performed in Italian cohorts.

Presence of the rheumatoid factor (RF) (12), a number ≤ 1 of TNF blockers previously failed (12), and the absence of the -174 CC IL-6 promoter genotype (13) were selected as clinical or genetic predictive factors of response to rituximab, based on the published literature. Patients carrying at least two of the aforementioned predictors were defined as "patients with predictors", while patients carrying ≤1 predictor of response were defined as "patients without predictors" below in the text and in the tables. These clinical and pharmacogenetic predictors were not considered separately, due to the small sample size. Methods of genetic analyses were described elsewhere (13).

Variables were reported as mean±SD or median (range), or as frequencies, as appropriate.

Comparisons between two groups of patients (i.e., "patients with predictors" vs. "patients without predictors") as regards demographic and clinical characteristics were made by using independent samples t-test, or Mann Whitney test for continuous variables, and chi square tests for categorical variables, as appropriate. Data were analyzed with SPSS software version 13.1. Results were considered statistically significant when $P < 0.05$.

RESULTS

Characteristics of the patients

The study cohort consisted of 66 patients (54 females, 81.8%; mean age 58±13 years; median disease duration 10 years, ranging from 2 to 51 years) suffering from RA (table 2). All RA patients complained of a high disease activity at the study entry, as measured by mean Disease activity Score on 28 joints (DAS28) (6.2±0.9), and HAQ-DI (1.8±0.6). All patients gave their informed consent to the study according to the Declaration of Helsinki, and the local Study Review Board approved the investigation. Patients were referred to 4 different rheumatologic Centres in Italy. Serologically, patients were 53/66 (80.3%) RF-positive and 50/66 (75.7%) anti-cyclic citrullinated peptides (anti-CCP)-positive (Table 2). All patients were treated with rituximab at the standard dose for RA in combination with methotrexate (81.8%) or other Disease Modifying Anti-Rheumatic Drugs (DMARDs) (leflunomide, cyclosporin A or hydroxychloroquine). The majority of patients (54/66, 81.8%) had been previously treated with one or more anti-TNF agents, while the remaining cases had been unresponsive to methotrexate alone or in combination with other DMARDs for at least 6 months. Primary or secondary inefficacy, rather than development of side effects, was the major reason for anti-TNF failures.

Globally, 96 courses of rituximab were administered in 66 patients during 12 months of follow-up (mean±SD: 1.45±0.56) (Table 2).

The cohort of 66 patients was then subdivided into two groups (Table 3): "patients with predictors" vs. "patients without predictors", as defined above. No significant differences were found between the two groups of patients as regards sex (p=0.22), disease duration (p=0.88), baseline disease activity evaluated by DAS28 (p=0.75), baseline disability (HAQ-DI) (p=0.24), while the group of patients with predictors showed an older age (p=0.01) (Table 3). A significant differences were observed as regards the presence of RF (p=0.001), the frequency of -174 CC IL-6 promoter genotype (p=0.02) and the number of TNF inhibitors previously failed (p<0.0001), as expected by the selection of the two groups.

Cost/utility results

Overall, 3.2 QoL gained and 9.5 QoL gained were calculated at month +6 and month +12, respectively, accounting for 0.05 QoL/patient gained and 0.14 QoL/patient gained at month +6 and month +12, respectively. Cost/QoL gained was € 115 500.00 at month +6 and € 56 589.50 at month +12.

In the group of patients with predictors (28/66 patients, 42.4%), 0.05 QoL/patient gained and 0.15 QoL/patient gained at month +6 and month +12 were respectively found, as well as cost/QoL of € 112 000.00 at month +6 and € 44 279.10 at month +12. Thirty-four courses of rituximab were administered in this group (1.21±0.42). By contrast, in patients without predictors (38/66 patients, 57.6%), 0.04 QoL/patient gained and 0.14 QoL/patient gained at month +6 and month +12, were

TABLE 2

CHARACTERISTICS OF THE PATIENTS	
FEATURES	ALL PATIENTS (N=66)
Age	58±13
Sex (F/M)	54/12
Disease duration (median, range) (yrs)	14.8±11.9 (10, 2-51)
Baseline DAS28	6.2±0.9
Baseline HAQ-DI	1.8±0.6
Positive RF	53/66 (80.3%)
Positive anti-CCP	50/66 (75.7%)
Positive -174 IL-6 CC genotype	7/66 (10.6%)
≤ 1 TNF blocker previously failed	35/66 (53%)
Total courses of RTX	96 (1.45/patient/year)

F: female; M: male; yrs: years; DAS28: disease activity score on 28 joints count; HAQ-DI: health assessment questionnaire disability index; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; IL-6: interleukin-6; TNF: tumour necrosis factor; RTX: rituximab. Values are expressed as mean±standard deviation

respectively found, as well as cost/QoL of € 125 176.50 at month +6 and € 66 769.23 at month +12. Sixty-two courses of rituximab were administered in this group (1.63±0.59) (Table 3). A significant difference was found as regards the number of cycles of rituximab administered in the two groups during one year of follow-up (p=0.003), with a higher number of courses in the group of patients without predictors (Table 3). Notably, the 6-month QoL gained and 12-month QoL gained were not statistically different between the two groups (p=0.85, and p=0.68, respectively).

DISCUSSION

In the present study, the long-term effect on utility and related costs of rituximab in RA were analyzed by focusing, for the first time, on the role of the predictive factors of response to rituximab in RA.

By coordinating a multicenter Italian researches on this topic, our group recently found that RF positivity, a lower number of TNF agents previously failed (12) and the absence of the -174 CC IL-6 promoter genotype (13) were associated with a good response to rituximab in RA within the first six months of therapy. These three predictors of response to rituximab were considered in the present work and integrated by defining "patients with predictors" those patients carrying at least two of the aforementioned predictors.

Herein we reported a pilot cost evaluation in a small real-life cohort of consecutive unselected patients, coming from 4 reference Centers for the cure of RA and other rheumatic diseases in Italy. Notably, the majority of pharmacoeconomic analyses in RA are constructed on series of patients recruited in worldwide sponsored protocols, who are very different from RA patients followed in clinical practice, due to a lower prevalence of comorbidities (23). Only one pharmacoeconomic evaluation in RA patients treated with rituximab was reported in literature,

TABLE 3

COMPARISONS BETWEEN "PATIENTS WITH PREDICTORS" AND "PATIENTS WITHOUT PREDICTORS"

FEATURE	"PATIENTS WITH PREDICTORS" (N=28)	"PATIENTS WITHOUT PREDICTORS" (N=38)	P VALUE
Age	64±11	57±12	0.01
Sex (F/M)	21/7	33/5	0.22
Disease duration (years)	15±13	15±11	0.88
Baseline disease activity (DAS28)	6.3±0.9	6.2±0.9	0.75
Baseline disability (HAQ-DI)	1.7±0.7	1.9±0.6	0.24
Positive RF	28/28	25/38	0.001
Positive anti-CCP	22/28	28/38	0.65
Positive -174 IL-6 CC genotype	0/28	7/38	0.02
≤ 1 TNF blocker previously failed	28/28	7/38	<0.0001
Total courses of RTX throughout first year	34 (1.21±0.42)	62 (1.63±0.59)	0.003

F: female; M: male; yrs: years; DAS28: disease activity score on 28 joints count; HAQ-DI: health assessment questionnaire disability index; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; IL-6: interleukin-6; TNF: tumour necrosis factor; RTX: rituximab. Values are expressed as mean±standard deviation

based on a real cohort of RA, confirming that costs/QALY gained were lower when rituximab was administered in earlier stages of treatment (24, 25), as reported by previous analyses (26) and also suggested by the present study, where one of the selected predictors was "≤1 TNF blocker previously failed".

In our work, a difference of more € 20 000 was observed as regards the 12-month cost/QoL between patients carrying predictors and patients without predictors. Thus, in a lifetime scenario, the presence of predictors of response to rituximab may account for a greater cost saving, and for a possible cost/QALY below the threshold of € 50 000 in RA (27-30). The value of this observation is reinforced by the difficult-to-treat cohort of RA patients herein reported (i.e., longstanding, very active disease), and by the older age observed in the group of patients showing the best results. Even better results should be expected in an Early Arthritis Clinic of RA patients (31, 32). Thus, the impact on cost-effectiveness of predictive factors of response to biologic therapies may be more evident in long-standing moderate to severe RA rather than in early RA, where the early diagnosis and treatment are the main determinants for the outcome (32); furthermore, the correct application of well established predictive factors of response may allow cost saving in the management of established RA, which still represents a large proportion of current clinical practice in rheumatology (33). On the other hand, not considering predictors of response in this setting of difficult-to-treat RA might result in unacceptable costs in the long term. Also, when considering the HAQ variations over a period in order to derive information about utility and related QALYs, it should be kept in mind that in long-lasting RA a relevant fraction of the HAQ score is irreversible due to structural anatomic damage, therefore the utility calculated only by HAQ may underestimate the real benefits of the therapies employed on the quality of life in this setting of RA patients. Notably, in this work we used predictors of response to rituximab calculated on the basis of clinical response to

rituximab within the first six months of follow-up after treatment, while the cost analyses were extended to one year of follow-up. Thus, while the clinical advantages of carrying predictors of response were described earlier (i.e. within the first six months after rituximab), the cost/utility gain was documented later (i.e., at one year of follow-up). In fact, QoL was not different between the two groups of patients both at month +6 and at month +12, while the number of rituximab courses in the first year of follow-up significantly differed. Thus, treatment with rituximab was equally effective on QoL in the two groups at one year, but a greater amount of rituximab was needed in patients lacking predictors to achieve this goal. Therefore, predictors of response seem to identify those patients less likely to relapse in the long term, while the absence of predictors may involve the need for more than one cycle of rituximab in the first year to reach the same QoL as that observed in patients with predictors. In this light, research should be focused on predictors of a good response in RA rather than a response in general (that also includes a moderate response), as well as on predictors of disease relapse after rituximab, to ensure greater cost savings in a lifetime scenario (34).

Certainly, our preliminary study showed some clear limitations, besides the retrospective nature of the design, and the cost analysis limited to rituximab costs. Our study did not take into consideration two or more alternatives, but it focused on the costs for patients having or not having predictors of response to rituximab and the possible reasons for the additional costs observed in patients not having predictors. In this work no answer to the question if it is worth while to ask for pharmacogenetic test in RA patients requiring rituximab was provided; however, the clinical usefulness of pharmacogenetic analyses in the management of biologic agents in rheumatic diseases in general is currently under evaluation, and the cost-effectiveness of such genetic analyses in routine clinical practice is not predictable at present. Also, the utility is generally applied to different health states and this requires a model, because several health states should be represented during time. In our paper the time horizon is the first year after rituximab therapy and the utility gained has been calculated by real HAQ scores at month +6 and +12 and based on the difference in QoL if compared to the baseline, while a pharmacoeconomic model with transitions into different health states are not computed. However this evaluation in a larger cohort of RA patients is ongoing, also comparing different regimens of treatment with rituximab (35).

In conclusion, the main suggestion of our study is that patients with longstanding RA carrying predictors of response need a lesser amount of rituximab than patients lacking predictors in order to achieve the same QoL at one year, since they showed a lower probability of undergoing retreatment after the first cycle of rituximab. Thus, using predictors of response, possibly also including pharmacogenetic markers, may represent a cost saving of rituximab use in established RA. Studies in larger cohorts and pharmacoeconomic models taking into account predictors of response should confirm these preliminary and retrospective observations.

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